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AB Transgenic mice expressing a major histocompatibility complex class II-restricted T cell receptor with specificity for a natural self-antigen, the fifth component of complement, were generated to analyze the mechanism of **tolerance** induction to a blood-borne self-protein. In the absence of C5 protein thymocytes from T cell receptor transgenic mice develop into mature **CD4** single positive cells which emigrate into the periphery and mount C5-specific T cell responses upon immunization with C5. In the presence of circulating C5 protein, **CD4** single positive thymocytes do not develop. Negative selection occurs late in thymic ontogeny leaving the bulk of **CD4**+8+ thymocytes unaffected. This phenotype may be due to a delay in contact with self-antigen presentation which, under physiological conditions, is inefficient in the cortex of C5+ mice, and therefore does not affect most immature double positive thymocytes. In contrast, in vitro exposure to C5(-)-presenting **dendritic** cells or in vivo injection of C5 peptide results in deletion of double positive thymocytes. C5+ transgenic mice are tolerant in vivo, but contain T cells in spleen and lymph nodes that secrete interleukin 2 and interferon gamma in response to C5 activation in vitro. When crossed onto a Rag1-/- background to prevent endogenous T cell receptor rearrangements, these peripheral potentially autoreactive cells do not appear. This indicates that endogenous T cell receptor rearrangements possibly leading to the expression of two receptors might be a prerequisite for their survival and export into the periphery.